II. Preliminary Remarks

This request for continued examination is filed in response to the Advisory Office Action mailed on August 4, 2009 for the above-identified patent application. The Advisory Office Action states that Applicants' claim amendment filed on July 17, 2009 in response to the Final Office Action of February 17, 2009 would require further consideration. *See* page 2 of the Advisory Office Action. Applicants file this request for continued examination and request that the amendment to claim 9 submitted on July 17, 2009 be entered and Applicants' arguments submitted in the response be considered. For Examiner's convenience, Applicants include the arguments below.

Applicants amend claim 9 and its dependant claims with this response to clarify that the recited structure for an antibody heavy chain variable domain is FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 and as was discussed on page 6 of the Applicants' response filed on November 3, 2008. This amendment does not introduce new matter and is fully supported by the specification as filed. *See* for example, paragraph [0005]:

> [0005] . . . The heavy chains have four domains, one corresponding to the V region and three domains (1, 2 and 3) in the C region . . . each V region is made up from three complementarity determining regions (CDR) separated by four framework regions (FR).

III. Patentability Arguments

1. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

A. Rejection Over *Dower* in view of *Taub*

Claims 9 and 13-17 continue to stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Dower* et al. U.S. Patent 5,427,908 filed May 1, 1990 and *Taub* et al. JBC 264(1): 259-265, 1989.

The Examiner explained at page 7 of the Office Action that this rejection is based on the Examiner's assumption that a "region" is a "domain." As discussed above, applicants amend the pending claims to clarify that they recite an antibody heavy chain variable domain with the structure of FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4. As discussed in Preliminary Remarks, this domain is made up of three complementarity determining regions and four framework regions in the order recited.

The Office Action alleges that *Dower* et al. teach methods of producing filamentous bacteriophage surface expressing binding domains of antibody fragments including VH that are encoded by nucleic acid sequences and screening the libraries of filamentous bacteriophage including fd, fl, and M13 expressing the VH and/or VL against various antigens, antigenic determinants, or haptens in order to select a specific binding domain. Emphasis added.

It is further stated in the Office Action that the main focus of *Dower* et al. is screening for VH and VL combinations. Emphasis added.

It is then stated that *Taub* teach screening for binding of heavy chain CDR domains particularly CDR3 including competitive binding assays. The Office Action then concludes that claims 9 and 13-17 would be obvious over the *Dower/Taub* combination because the substitution

of one known element (phage-displayed VH-VL as taught by *Dower* et al.) for another (i.e. CDR alone as taught by *Taub* et al.) would have yielded predictable results (i.e. binding to epitopes/antigens) to one of ordinary skill in the art at the time of the invention.

Applicants respectfully disagree with this conclusion because the structures in the cited art referred to by the Examiner differ from those presently claimed by the amended claims. A CDR and a variable domain are two different structures. The term of art "variable domain" is reserved for the structure "FR1-CDR1-FR2-CDR2-FR3-CDR3- FR4" which is made up of three complementarity determining regions (CDR1, CDR2 and CDR3) and four framework regions (FR1, FR2, FR3 and FR4) arranged in the order recited.

Dower discloses:

> When the protein of interest is an antibody of a desired binding specificity, the antibody may be of any of the known isotypes or subclasses for a particular species, and may be a single-chain or two-chain binding complex or portion thereof. For instance, only the variable antigen-binding regions of heavy (V_H) and/or light (V_L) chains ***may be identified and cloned; the binding fragments (F_v) or Fab encoded thereby may find use either as a binding fragment, joined to constant regions of heavy or light chains, or joined to other proteins having desired effector functions***. The characteristics of the constant region domains will depend to a large extent on the use intended for the antibody, e.g., diagnostic and/or therapeutic applications, catalytic antibodies, etc.

(Emphasis added.)

This passage does not state that the binding domain consists of an "...antibody heavy chain variable domain..." as required by the pending claims. The passage provides that ...V_H and/or V_L chains may **be identified and cloned**. It then states that,

> *...the binding fragments (F_v) or Fab encoded thereby may find use either as a binding fragment, joined to constant regions of heavy or light chains, or joined to other proteins having desired effector functions.*

F_V fragments consist of both a heavy chain variable region (V_H) and a light chain variable region (V_L) which together form an antigen binding site. *See* e.g. Figure 1 of the present application. Fab fragments consist of a V_L and a V_H, each of which (unlike the heavy chain variable domains of the present invention) comprises a constant region which when combined constitute an antigen binding fragment. *Id.* The passage in *Dower* referred to by the Examiner does not state that a heavy chain variable domain is a binding molecule. **It refers to the combination of V_H and V_L that gives rise to the F_V and/or Fab binding fragments.**

The cloning of V_H and/or V_L domains and their combinations are further elaborated in *Dower*, column 4, lines 51-64 where the use of separate cloning vectors for antibody light and heavy chain sequences is suggested from which a combinatorial library is constructed to bring together V_H and V_L domain sequences in associated pairs to form binding domains. Thus, *Dower* discloses that its method is useful for identification and cloning of a new variable V_H domain and V_L domain **which can be used to form F_V or Fab antigen** binding fragments and does not disclose the display of a binding molecule consisting of a V_H domain on the surface of a filamentous phage.

This interpretation is further supported by the fact that the claims of *Dower* are directed to screening a DNA library for nucleotide sequences which encode,

> ...an antibody Fab fragment comprising first and second polypeptide chains, one chain comprising a light chain variable region and another chain comprising a heavy chain variable region... (See claim 1)

Further, Example 1 of *Dower* is similarly directed to display of Fab molecules, in which one polypeptide chain composed of V_H and C_H domains is presented as a fusion with bacteriophage gene III protein and displayed with an associated second polypeptide composed of

V_L and C_L domains to provide a binding domain formed by the combination of V_H and V_L chains and their associated constant regions together.

In summary, *Dower* does not disclose the display of an antibody heavy chain variable domain as required by the present claims.

At page 6 of the Office Action, it is stated that "the claim is obvious because the substitution of one known element (phage-displayed VH-VL as taught by *Dower* et al.) for another (i.e. CDR alone as taught by *Taub* et al.) would have yielded predictable results." Thus, the Examiner has concluded that the pending claims are obvious over the *Dower/Taub* combination based on factual assumption that all elements of the pending claims were known to a person skilled in the relevant art after reading *Dower* and *Taub.* As discussed above, the CDR of *Taub* and an antibody heavy chain variable domain of the pending claims as currently amended are two different structures.

Applicants respectfully bring to the Examiner's attention Section 2143 of MPEP, which provides:

> To reject a claim based on combining prior art elements according to known methods to yield predictable results, Office personnel must resolve the *Graham* factual inquiries. Then, Office personnel must articulate the following:
>
> (1) *a finding that the prior art included each element claimed*, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference; . . .
>
> MPEP, Section 2143(A) (emphasis added).

As explained in detail above, the *Dower/Taub* combination fails to disclose a binding domain which consists of an antibody heavy chain variable domain, as recited by the pending claims. Therefore, the subject matter of the pending claims is not obvious over the *Dower/Taub*

combination, and the rejection of the pending claims under 35 U.S.C. §103(a) may be property withdrawn; and withdrawal is respectfully requested.

V. Conclusion

In view of the above arguments, Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at (312) 846-5622.

Respectfully submitted,

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